REMARKS

Status of the Claims and Amendment

Claims 1, 15, and 18-20 have been amended. Claims 1-21 are all the claims pending in this application. Claims 10 and 12 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-9, 11 and 13-21 are rejected.

Claim 1 has been amended as suggested by the Examiner in response to a claim objection, and in response to the indefiniteness rejections under 35 U.S.C. 112, second paragraph.

Claims 15 and 18-20 have been amended to replace "from" with "for". Claim 20 has also been amended to recite that the method involves administering "to a patient" at least a single dose of a drug.

No new matter is added.

Information Disclosure Statement

Applicants thank the Examiner for consideration of reference number 1 in the Information Disclosure Statement filed January 6, 2004, by returning an initialed and signed PTO/SB/08 form submitted therewith. With regard to reference number 22, the Examiner has not indicated consideration of this reference because the publication date cannot be found.

In response, Applicants submit herewith a PTO/SB/08 form with the full reference citation including the publication date.[1] The Examiner is respectfully requested to consider the reference by returning an initialed and signed PTO/SB/08 form.

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[1] Applicants note that the page numbers of the reference as presented in the previous IDS was inadvertently miscited to be pages "571-578", but should be pages "543-555", as correctly presented in the PTO/SB/08 form submitted herewith.

Response to Claim Objections

Claim 1 is objected to by the Examiner because step d) of claim 1 recites, "one dose escalation steps" and should read "dose escalation step" to be grammatically correct.

In response, Applicants have amended claim 1 as suggested by the Examiner.

Withdrawal of the grounds of objection is respectfully requested.

Response to Claim Rejections Under 35 U.S.C. § 112

Claims 1-9, 11, 13, 14 and 20 are rejected under 35 U.S.C. § 112, second paragraph, as being allegedly indefinite for the following reasons.

1. The Examiner asserts that step f) of claim 1 reciting "checking the drug for cumulative effects after administration and providing this information to the computer model" is unclear as to how to check the drug for cumulative effects. The Examiner appears to suggest amending step f) to recite "checking the patient for cumulative drug effects after administration."

In response, and solely to advance prosecution of the present application, step f) of claim 1 has been amended as suggested.

2. The Examiner asserts that step j) of claim 1 is unclear because of the recitation "performing at least one phase III clinical trial for step h) chosen clinical indication by step i) chosen regimens." The Examiner requests clarification as to whether Applicants intended the phase III clinical trial to be performed such that the clinical indication from step (h) is assessed by implementing the optimal regimen from step (i).

In response, Applicants believe that it is clear from the claim that the phase III clinical trial executed in step (j) is performed using the regimen from step (i) on the indication from step (h). Nevertheless, and solely to advance prosecution of the present application, step j) of claim 1

has been amended to further clarify and recite "performing at least one phase III clinical trial for a clinical indication chosen in step (h) using a regiment that was chosen in step (i)."

3. The Examiner asserts that the relationship between step k) and the previous method steps is unclear from the recitation "performing at least one phase IV clinical trial for post-marketing subpopulation analysis and long term product safety." The Examiner appears to asserts that claim language tying this step to previous steps is missing.

In response, and solely to advance prosecution of the present application, step k) of claim 1 has been amended to recite "performing at least one phase IV clinical trial, based on at least one previous clinical trial, for post-marketing subpopulation analysis that may identify differences in efficacy and toxicity between the subpopulations, and in long term product safety assessment."

4. The Examiner asserts that the recitation "administering at least a single dose of a drug to obtain data from performing" in claim 20 is unclear as to how "to obtain data from performing a phase IV clinical trial". The Examiner requests clarification as to whether Applicants intended the claim to read "to obtain data for performing a phase IV clinical trial."

In response, and solely to advance prosecution of the present application, claim 20 has been amended to recite "to obtain data for performing a phase IV clinical trial".

Withdrawal of the above rejections under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Response to Claim Rejections Under 35 U.S.C. § 103

Claims 1-9, 11, and 13-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the CDER Handbook (from Department of Health and Human Services, FDA. http://www.fda.gov/cder/handbook/The CDER Handbook), in view of Berry (*BioPharmaceutical*

Report 9(2): 1-11 (2001)) and in further view of view of Holford *et al.* (*Ann. Rev. Pharmacol. Toxicol.*40: 209-234 (2000)) and Veyrat-Follet *et al.* (*Clin. Phamacol. Ther.* 68: 677-687 (2000).

With regard to claims 1, 13, and 15-19, the Examiner asserts that the CDER handbook provides new drug development guidelines as determined by the Food and Drug Administration of the United States (FDA), and outlines the procedures for the new drug development process which includes animal testing and progression from pre-clinical to Phase III clinical studies as well as determination of a stop-trial decision if the risk is determined to be too great (claims 3 and 9).

Berry appears to be asserted for teaching that Phase I clinical trials involve dose escalation and the determination of a maximum tolerated dose (MTD), Phase II trials involve optimal dose determination for determining the move to Phase III trials , and stopping trial if the drug is determined to be ineffective to continue. Berry is also asserted to teach models for clinical trials in which algorithms may be adjusted in response to data during the trial and between trials. The Examiner admits that the CDR Handbook and Berry do not teach a computer model for clinical trial design.

Holford appears to be asserted for teaching computer simulations for building a computer model based on dose response relationships, and that the computer simulations may be used to define responses in clinical trials for drug development purposes.

Veyrat-Follet is asserted to further illustrate the implementation of a clinical trial simulation, by teaching that clinical trial simulation is based on pharmacokinetic and pharmacodynamic models for streamlining drug development. With regard to claims 4, 5, 7, 8, and 11, Veyrat-Follet is asserted to teach determination of subpopulations based on clinical trial simulations in different clinical Phase II trials.

Thus, the Examiner appears to conclude that it would have been *prima facie* obvious, and one of ordinary skill in the art would have been motivated to implement the pre-clinical to Phase IV clinical trials outlined by the FDA in the CDER handbook for newly tested drugs, with the model algorithms of Berry that may be adjusted according to data obtained from the trials, and to include computer simulation for each step of the trial design as taught by Holford and by Veyrat-Follet to provide a streamlined and efficient drug design.

In response, Applicants assert that the Examiner has failed to establish a *prima facie* case of obviousness for at least the following reasons.

Neither the CDR Handbook, Berry, or Holoford, separately or combined, teach or suggest all the claim limitations." M.P.E.P. § 2143. None of the cited documents teach or suggest the presently claimed method of performing interactive clinical trials in which a computer model or *in silico* patient is created, or adjusting the computer model or *in silico* patient and computer simulations based on the results of the clinical trial.

The CDR Handbook merely describes the drug development process from pre-clinical to NDA (New Drug Application) review, and is the FDA's guideline for meeting the statutory requirements for compliance with regard to drug efficacy and safety (from pharmacology and toxicology data) for each stage of the drug development process. In this respect, although the CDR Handbook provides instructions and procedures regarding the way preclinical and clinical trials are to be designed and executed throughout the development, the CDR Handbook does not teach or suggest the presently claimed method of performing interactive clinical trials in which a computer model or *in silico* patient is created, or adjusting the computer model or *in silico* patient and computer simulations based on the results of the clinical trial.

Accordingly, even though Applicants' claimed method complies with the FDA's guidelines in the CDR Handbook, the CDR Handbook does not render Applicants' presently claimed method obvious, nor serve as a sufficient basis to motivate one of ordinary skill in the art to combine these guidelines with Berry to obtain the presently claimed method.

The Berry article, entitled "Adaptive Trials and Bayesian Statistics in Drug Development", is a review of statistical methods used for the design and during execution of clinical trials. Specifically, Berry refers to the implementation of Bayesian statistics methods during clinical development. Aside from the common aid to streamline drug development, the methods described in Berry are different from the claimed method because Berry refers to completely statistical methods that serve as a different ***alternative*** to the methods of the claimed invention. In this respect, many different alternative methods have been set forth in the art to streamline drug development.

The difference between the claimed interactive clinical trial design method and an adaptive trial design method such as that described in Berry is discussed at paragraphs [0163]-[165] of the present published application, which states that:

> IV.B. Interactive Clinical Trial Design as compared to the Adaptive Trial Design method
>
> "Adaptive designs are dynamic". They are based on the assumptions of Bayesian statistics (in contrast to the classical design, which is based on frequentists assumptions). Adaptive design trials suggest an improvement to the classical design, as they offer ability to stop trials relatively early, drop or add treatment groups, change group proportions or shift seamlessly into a later phase, etc. These models aid in planning trials by predicting the probability distribution of trial outcomes conditional on current knowledge and assumption, and thus evaluating the ability of the trial to support a certain decision. These models rely upon prior probability distribution (*e.g.* FIG. 3) [30-33].
>
> By comparing FIG. 3 to FIG. 1, one can immediately notice the main differences between the two methods: (a) the point of influence of the Interactive Design can be as early as the Pre-clinical stage, whereas to the point of influence of the Adaptive Design begins only in Phase-II; (b) moreover, while the first and

> potentially most important decision-making impact of the Interactive Trial Design takes effect already at the end of Phase-I, the Adaptive Trial design's impact can be effectuated only towards the end of Phase-III. The reason for these differences lies in the significant distinction between the tools employed by each of the designs. A major asset offered by the disclosed technique is its predictive power, rather than the improved data analysis methods, offered by the Adaptive Design. In other words, the disclosed design is primarily prospective, integrating all the available biological, medical, pharmacological, theoretical and clinical information. In contrast, Adaptive design is primarily retrospective, integrating statistical methods with the information from the clinical trials.

In particular, an important difference is that the Bayesian statistical method of Berry does not include a mathematical model or an *in silico* patient, as acknowledged by the Office Action at page 7, 2nd paragraph of the Office Action.

Another significant distinction between the claimed interactive clinical trial design method of the present invention and the adaptive clinical trial design of Berry is the predictive power offered by the claimed invention. In contrast, the adaptive design improves data analysis methods, and does not offer predictive ability. The Bayesian statistical method of Berry performs data analysis as the data is accumulated from the clinical trial and assigns doses based upon prior probability distribution on a dose-response curve. See page 3, 2nd column, last paragraph to page 4, 1st column, 2nd paragraph of Berry. In other words, the claimed interactive clinical trial design method of the present invention is primarily prospective, integrating all the available biological, medical, pharmacological, theoretical and clinical information, while the adaptive trial design method of Berry is primarily retrospective, integrating statistical methods with the information from the clinical trials. See paragraph [0165] of published application.

Accordingly, even if one of ordinary skill in the art would have somehow been inclined to combine the CDR Handbook and Berry, which would not be the case, the Examiner has acknowledged that the combination of the CDR Handbook and Berry do not teach or suggest a

computer model for clinical trial design. Also, the adaptive trial design method of Berry is not the same as the interactive trial design of the presently claimed method, as discussed above.

Holford does not cure the deficiencies of the CDR Handbook and Berry. Holford is merely a review article that provides a general description of the use of computer simulations in clinical trials. See page 210, last sentence of 1st full paragraph of Holford. Although Holford teaches that computer simulation is the process of building a mathematical model that mimics a real-world situation, none of the simulation models described in Holford (see pages 215-217 of Holford) are mechanistic mathematical models that resemble the claimed computer model or *in silico* patient of the present invention. In this respect, even though Holford shows examples including PK/PD models (such as NONMEM; see Table 3 of Holford), these models are not models for disease dynamics. In contrast, two important components of the claimed invention are the mathematical models for pathology dynamics and the mathematical models for physiology dynamics. Accordingly, Holford merely provides a general teaching of simple mathematical models that may provide a solution to a specific issue during drug development, but no specific or practical teaching that would guide one of ordinary skill in the art to the presently claimed method that provides a comprehensive systematic solution, as illustrated, for instance, in Figure 5 of the present application.

Similarly, Veyrat- Follet teaches the use of a PK/PD model to predict the effect of high dose of docetaxel on a subpopulation of non-small-cell lung cancer patients, having high baseline alpha1-acid glycoprotein (AAG) levels (See Abstract and page 678, paragraph bridging 1st and 2nd column of Holford). The PK/PD model of Veyrat- Follet is adjusted based on the results of phase II clinical trials with 151 patients that were administered 75 or 100 mg/m^2 of docetaxel once every 3 weeks. However, the Veyrat- Follet model is a nonlinear mixed effects PK/PD

model that does not include a model for disease dynamics. Moreover, the Veyrat- Follet PK/PD model is combined with known statistical methods to classify the patient in the trial.

Specifically, the modeling in Veyrat- Follet is described as follows:

> pharmacokinetic and pharmacodynamic models for time to progression, time to death and time to drop-out were developed and evaluated. These several dose response models, when combined with models for the distribution of covariates in a target population and a particular study design, allow clinical trial simulation for that design. We then evaluated the simulation process (as a tentative of a validation step) with the use of the phase II data by comparing predicted trial results obtained by means of simulation with the actual phase II trial outcomes. After successful validation, in a final step, a phase III trial in which 100 mg/m^2 of docetaxel was compared with 125 mg/m^2 of docetaxel in patients with high AAG could be simulated.
> See page 678, 2nd column, 1st paragraph of Veyrat- Follet.

Further, as disclosed at page 679, 1st column, 2nd and 3rd paragraph of Veyrat- Follet:

> Model building. Clinically important endpoints for the ultimate clinical trial simulation are progression and overall survival. A parametric survival model (with time-dependent covariates) was used for these endpoints for a predictive model. Because 21% of the patients dropped out before the cut-off date of the analysis, drop-out was considered to be a competing risk, for which a time-to-event model was also developed. For this model, patients who died and patients who were alive at the cut-off date were censored.
>
> Separate hazards were estimated for each event type. Different types of hazard models (exponential, Gompertz, and Weibull) were tested.[17] The Laplacian estimation method as implemented in the nonlinear mixed effect model program was used to provide maximum likelihood estimates of the model parameters.18 Model selection was based on the change in the log-likelihood criterion. The Weibull model was found to provide the best fit (data not shown). Accordingly the log hazard for these 3 events was specified as follows:
>
> $$\log(\lambda(t,\theta)) = \theta_1 + \theta_2 \log(t) + \sum_{i=3}^{n} \theta_i X_i(t)$$
>
> in which $\theta = (\theta_1, \theta_2, ..., \theta_n)$ is a vector of parameters and X is a vector of covariates."

Based upon the information provided in the model, the investigators of Veyrat- Follet made a simple extrapolation according to their assumed PD model and suggested that higher

doses are not cost effective. However, because the model of Veyrat-Follet lacks information about the actual effect of higher doses of the drug, this extrapolation is inconclusive.

With regard to claims 4, 5, 7, 8, and 11, and the Examiner's assertions that Veyrat-Follet teaches determining subpopulations based on clinical trial simulations in different phase II trials (see bottom of page 7 of present Office Action), Applicants note that the subpopulation of high AAG was determined ***prior*** to the onset of the computer simulations, based on clinical information. See page 678-680. As discussed above, Veyrat-Follet "evaluated the simulation process (as a tentative of a validation step) with the use of the phase II data by comparing predicted trial results obtained by means of simulation with the actual phase II trial outcomes." See page 678, 2nd column, 1st paragraph of Veyrat- Follet. Accordingly, although an alternative dosing regimen was clinically tested (phase II) on this subpopulation and an alternative regimen was simulated, the simulation results were compared to the actual clinical phase II results. Then, using the PK/PD model, clinical phase III trial was simulated and the results obtained by Veyrat-Follet indicated that the benefit of the alternative regimen was not significant, as described below:

> The low power to detect a difference due to dose intensification was the basis for the decision not to perform such a trial. The simulation exercise yielded valuable insight into how pharmacokinetic- and pharmacodynamic-based simulation of clinical trials may have an impact on decision making in drug development. See Abstract.

Also, "although the simulated trial showed a trend toward higher efficacy, higher survival in the 125-mg/m2 arm compared with the standard regimen of 100 mg/m2, the difference was only significant in 6 of 100 trials, this indicated that we would be unlikely to be able to show a useful benefit." See page 686, sentence bridging 1st and 2nd columns of Veyrat-Follet. Based

upon the results of Veyrat-Follet, one of ordinary skill in the art would have concluded that simulations would be insufficient to help drug development.

Thus, although Holford and Veyrat-Follet used computer simulations for clinical trials, both are evidence that the art at that time did not recognize using a systematic method as claimed for performing interactive clinical trials in which a computer model or *in silico* patient is created, or adjusting the computer model or *in silico* patient and computer simulations based on the results of the clinical trial. Instead, the teachings of Holford and Veyrat-Follet demonstrate that at the time the invention was made, one of ordinary skill in the art was guided and inclined to perform adaptive trial designs which offered an advantage over classical design because the trials offered the ability to stop trials early if the drug is determined to be ineffective. That is, the computer simulations integrated statistical methods to analyze data accumulated from clinical trials in order to assign doses based upon prior probability distribution on a dose-response curve.

Accordingly, one of ordinary skill in the art would not have been motivated to combine the teachings of Holford and Veyrat-Follet with the CDR Handbook and Berry in order to obtain the presently claimed method.

However, even if one of ordinary skill in the art was somehow inclined or motivated to combine the teachings of the CDR Handbook, Berry, Holford, and Veyrat-Follet, which would not be the case, one of ordinary skill in the art would not obtain the presently claimed method for performing interactive clinical trials in which a computer model or *in silico* patient is created, or adjusting the computer model or *in silico* patient and computer simulations based on the results of the clinical trial. This is because the CDR Handbook merely provides instructions and procedures regarding the way preclinical and clinical trials are to be designed and executed throughout drug development. Berry discloses an ***adaptive*** trial design method that is distinct

from the ***interactive*** trial design of the presently claimed method because the method of Berry is based upon assumptions of Bayesian statistics. Similarly, Holford and Veyrat-Follet use of computer simulations that integrate statistical methods to analyze data accumulated from clinical trials in order to assign doses based upon prior probability distribution on a dose-response curve.

In summary, the combination of CDR Handbook, Berry, Holford, and Veyrat-Follet do not teach or suggest all the inventive step(s) of the claimed method, and the combination would not result in the presently claimed invention, nor render all the inventive step(s) of the claimed method obvious.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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